IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

TEVA PHARMACEUTICALS USA, INC., Plaintiff, vs. AMGEN INC., Defendant.	CIVIL ACTION No. 2:09-cv-05675-SD Hon. Stewart Dalzell, U.S.D.J.
AMGEN INC., and AMGEN MANUFACTURING, LIMITED, Counterclaim Plaintiffs, vs. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD., Counterclaim Defendants.	

AMGEN INC.'S CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

The patent claims at issue in this case claim the products and methods of treatment made possible by Dr. Larry Souza's pioneering inventions relating to a human protein now commonly called granulocyte-colony stimulating factor or simply "G-CSF."[1] U.S. Patent No. 5,580,755 ("the '755 patent") claims polypeptide products first made available by Dr. Souza's inventions. U.S. Patent No. 5,582,823 ("the '823 patent") claims novel methods of providing therapy by administering the recited polypeptide products.

Because the asserted patent claims define the claimed polypeptide products by reciting particular amino acid sequences,[2] which are present in both Amgen's and Teva's products, the construction of only a few claim terms is in dispute. Teva filed this lawsuit to challenge the validity of Dr. Souza's patents, and so proposes constructions that seek to blur the line between Dr. Souza's claimed inventions and the prior art. As demonstrated below, however, Amgen's proposed constructions rely on the plain meaning of claim terms – meanings that were undisputed and consistently applied in the patent specification and the prosecution histories. In contrast with Teva's proposals, the intrinsic record establishes that Dr. Souza's claimed products and methods, which made effective granulocytopoietic therapy possible for millions of cancer

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[1] Granulocytes are a form of white blood cells that can mature into neutrophils, the white blood cells that helps the body fight infections.

[2] Amino acids are the building blocks of polypeptides and are recited in the claims-in-suit by their three letter abbreviation. A polypeptide is a string of amino acids linked together by peptide bonds – like pearls on a necklace. Proteins are comprised of polypeptides and typically entail further modifications to the polypeptide, such as the addition of sugar chains to the polypeptide, the formation of additional bonds between amino acids within the polypeptide, causing it to assume a unique three-dimensional shape, or the modification of side chains of specific amino acids within the polypeptide. Proteins carry out vital functions in the body. Amgen will provide further explanation of the relevant technology at the claim construction hearing.

patients, were clearly distinguished from the therapeutically useless polypeptide preparations of the prior art.

A. The State of the Art Before Dr. Souza's Inventions

Prior to Dr. Souza's inventions, there was a long-felt need within the medical community for an effective treatment for a serious blood disorder called neutropenia. Neutropenia occurs when there is an abnormal and dramatic decrease in the number of certain white blood cells, called neutrophils,[3] that help the body fight infections. A variety of causes can lead to neutropenia, one of which is the use of chemotherapy to treat cancer patients. Chemotherapy regimens are toxic to many rapidly growing cells in the body and do not discriminate between rapidly growing cancer cells and other rapidly growing cells, such as progenitor blood cells (*e.g.*, granulocytes) from which neutrophils are formed. Consequently, cancer patients receiving chemotherapy or bone marrow transplants often suffer a dramatic and prolonged depletion in their neutrophil levels which increases their susceptibility to infection, potentially leading to hospitalization, the need for intravenous antibiotics, decreased or withheld chemotherapy treatment, and even infection-related death.

Before Dr. Souza's inventions, no one had successfully obtained or made an isolated human G-CSF polypeptide product that could effectively treat neutropenia. There were a few reports of preparations of proteins that had been obtained from certain human cancer cells that reportedly stimulated the formation of granulocytes and other blood cell types in laboratory tests. These preparations were alternately called "pluripoietin," "pluripotent CSF," or "CSF-ß."[4] Very little information was known about the identity or chemical structure of any polypeptides within

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[3] Neutrophils are a type of granulocyte, which are white blood cells characterized by the presence of granules in their cytoplasm.

[4] Ex. 1 ('755 patent, col. 2:4-60). All citations to the column and line numbers of the specification will be to the '755 patent since the patents-in-suit share a common specification.

these preparations. Moreover, because these preparations were obtained from human cancer cells, they not only contained a variety of different proteins and other molecules, but the products these cancerous cells produced were considered to be unsuitable for use as therapeutic products for treatment of patients. Nor did these preparations enable skilled artisans to identify the amino acid sequences of the polypeptides they contained, to isolate and identify the DNA sequences encoding those polypeptides, or to produce and isolate useful quantities of the active substances they apparently contained.

B. Dr. Souza's Path-Breaking Inventions

In 1985, Dr. Souza succeeded in isolating and sequencing DNA that encodes a species of human G-CSF. He then used the DNAs to identify the complete amino acid sequence of a human G-CSF polypeptide and to make genetically engineered cells capable of producing that polypeptide in sufficient quantity and quality for effective therapeutic use. Through this succession of inventions, culminating in the recombinant production and isolation of a therapeutically useful human G-CSF polypeptide, Dr. Souza provided medical practitioners with the long-sought ability to treat a variety of medical disorders associated with neutropenia.[5] Dr. Souza's work also resulted in a number of U.S. patents issuing in his name and assigned to his employer, Amgen. Two of those patents – the '755 and '823 patents – are at issue here.

Using Dr. Souza's path-breaking inventions, Amgen developed NEUPOGEN® — a commercial embodiment of the polypeptide product claimed in Dr. Souza's '755 patent, and the first human G-CSF pharmaceutical composition approved by FDA for the treatment of neutropenia. Amgen's development of NEUPOGEN® was widely recognized as a major medical advance, one praised by Dr. David Kessler, then FDA commissioner, as "a pioneer

[5] *See* Ex. 2 (Foote and Boone, "Chapter 4: Biopharmaceutical Drug Development: A Case History," *Biopharmaceutical, Industrial Perspective* (1999)) (providing overview of G-CSF and its therapeutic activity).

therapeutic product" that "will be useful in treating a large number of cancer patients."[6] And indeed it was. In the first year after approval, nearly 200,000 cancer patients, whose white blood cell levels were suppressed by the chemotherapy they received, benefited from NEUPOGEN®'s use in conjunction with their chemotherapy.[7] And since that time, millions more patients have been effectively treated using Amgen's human G-CSF product.

Dr. Souza and Amgen received widespread public acclaim for these inventions. In 1994, the President of the United States of America awarded Amgen the National Medal of Technology, the Nation's highest honor for technological achievement, partly in recognition of "the pioneering work of Dr. Lawrence M. Souza" that identified "the DNA code for a protein that stimulates the production of neutrophils."[8] In 1991, NEUPOGEN® was awarded the Prix Galien by an independent jury of medical experts as the most outstanding product of the year for its medical efficacy, safety and innovation.[9] NEUPOGEN® was also recognized as a Product of the Year by Fortune Magazine,[10] and Dr. Souza was recognized in 1992 as a Distinguished Inventor by the Intellectual Property Owners Association.[11]

C. Amgen's Dispute with Teva

Even Teva has acknowledged the innovative nature of Dr. Souza's inventions. Rather than investing in research and development to create a new and improved polypeptide, or even

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[6] Ex. 3 (New Drug Fights Infection in Cancer Patients) at AMT_00068385.

[7] Ex. 4 (Amgen Annual Report 1992) AMT_00014780-835 at AMT_00014784.

[8] The Presidential Citation to Amgen reads: "For its leadership in developing innovative and important commercial therapeutics based on advances in cellular and molecular biology for delivery to critically ill patients throughout the world." Ex. 5 (1994 National Medal of Technology) AMT_00068238-258 at AMT_00068243.

[9] Ex. 6 (1991 UK Prix Galien awarded for Neupogen® to Amgen Roche) AMT_00068225-230 at AMT 00068225.

[10] Ex. 7 (Fortune Products of the Year) AMT_00068261-266 at AMT 00068265.

[11] Ex. 8 (3/27/1992 Letter from Donald W. Banner to Lawrence M. Souza) AMT_00068267-271 at AMT 00068267.

an alternative treatment option, Teva elected to copy NEUPOGEN® and cash in on its success. Teva has acknowledged NEUPOGEN® as the "innovator" product,[12] characterized its product as a "biogeneric,"[13] and admitted that the sale and/or use of Neutroval in the United States will infringe Amgen's asserted patents.[14]

In this lawsuit, Amgen seeks a declaratory judgment that the importation, manufacture, offer for sale, sale and/or use of Teva's generic human G-CSF product in the United States will infringe Amgen's asserted patents. Having admitted it will infringe, Teva seeks to avoid the consequences of its infringement by arguing that the asserted claims are invalid. Toward that end, Teva seeks to construe the claims in a manner that covers and does not distinguish the prior art. Teva, however, should not be allowed to stretch Amgen's patent claims to encompass prior art preparations that were disclosed to and considered by the U.S. Patent and Trademark Office ("Patent Office"), and expressly distinguished during interference and prosecution proceedings. As the intrinsic record demonstrates, the Patent Office granted the asserted '755 and '823 claims after years of careful scrutiny precisely ***because*** Dr. Souza's claims are limited to the particular

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[12] Ex. 9 (2/21/2008 Teva Press Release) AMT_00068353-354 at AMT 00068353.

[13] Teva USA's Amended Answer to Amgen's Counterclaims (Docket No. 47) at ¶ 18; Teva Ltd.'s Amended Answer to Amgen's Counterclaims (Docket No. 48) at ¶ 18 ("Teva Ltd. admits that according to BLA No. 125,294, Teva USA's proposed Filgrastim product for the U.S., NEUTROVAL™, it the same Filgrastim product that is sold in Europe under the trademark TevaGrastim®. . . . Teva Ltd. also admits that a January 12, 2009 presentation at the 27th Annual Healthcare Conference states 'Tevagrastim®, first biogeneric launch in Europe.").

[14] *See* Teva USA's Amended Answer to Amgen's Counterclaims (Docket No. 47) at ¶ 29; Teva Ltd.'s Amended Answer to Amgen's Counterclaims (Docket No. 48) at ¶ 29 ("Teva Ltd. admits that sale and/or use of Teva's Filgrastim product in the U.S. for the reduction of severe neutropenia and the incidence of febrile neutropenia in patients treated with established myelosuppressive chemotherapy for cancer, to the extent such use is not exempted under 35 U.S.C. 271(e)(1), will infringe certain claims of the '823 and '755 patents, to the extent those claims are found valid and enforceable. Teva Ltd. is without information or believe [sic] as to which claims of the '755 and '823 patents Amgen asserts are infringed, and therefore denies the remaining allegations of paragraph 29.").

species of human polypeptides specifically recited in the claims and do not encompass the prior art preparations.

II. THE ASSERTED CLAIMS OF THE '755 AND '823 PATENTS

The asserted claims of the '755 patent relate to an isolated species of human polypeptide, designated in the claim as "human pluripotent granulocyte colony stimulating factor (hpG-CSF)."[15] The claimed species of human polypeptide is specifically defined by reference to a core sequence of 174 amino acids, which was first determined by Dr. Souza when he isolated a DNA encoding human G-CSF. This was the first elucidation of the primary structure of any human G-CSF. While another less-active species of human G-CSF with 177 amino acids was later discovered by other scientists,[16] Dr. Souza's claim is expressly limited to polypeptides with the recited 174 amino acid sequence, and specific variations of that sequence: a sequence in which a methionine amino acid is added at the -1 position (the beginning of the sequence), and analogs of these sequences in which one or more cysteine amino acids at recited positions are replaced by a serine amino acid.

> Claim 1 of the '755 patent: An isolated human pluripotent granulocyte colony stimulating factor (hpG-CSF) polypeptide having an amino acid sequence selected from the group consisting of:

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[15] Subsequent to Dr. Souza's patent filing in August 1985, the common designation for the claimed polypeptides became simply "G-CSF" or "human G-CSF."

[16] Ex. 10 (Nagata et al., "Molecular cloning and expression of cDNA for human granulocyte colony-stimulating factor," *Nature* 319:415-417 (1986)) AMT_00011216-218.

+1 +10 +20
Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln

+30 +40
Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys

+50 +60
Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

+70 +80
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser

+90 +100
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly

+110 +120
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln

+130 +140
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

+150 +160
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe

+170 +174
Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro;

and

-1 +1 +10 +20
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln

+30 +40
Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys

+50 +60
Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro

+70 +80
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser

+90 +100
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly

+110 +120
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln

+130 +140
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe

+150 +160
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser Phe

+170 +174
Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro;

and analogs thereof wherein one or more cysteines residues located at positions 17, 36, 42, 64, and 74 are replaced by serine.[17]

[17] As depicted in the claims, the amino acid sequence is listed by reference to the three letter abbreviation for the amino acid; e.g., the claimed sequence begins with Thr (threonine), Pro (proline), Leu (leucine), Gly (glycine) and so forth. For brevity, the recited amino acid sequences will be subsequently short-handed herein as "[1-174]; and [Met 1-174]; and serine replacement analogs."

> Claim 2 of the '755 patent: A composition comprising the hpG-CSF polypeptide of claim 1 and a carrier.

The '823 patent claims relate to the use of "hpG-CSF" in novel methods of treatment. Claim 2 of the '823 patent claims a method for providing granulocytopoietic therapy (*i.e.*, therapeutic treatment that stimulates the production of granulocytes by administering "hpG-CSF."

> Claim 2 of the '823 patent: A method for providing granulocytopoietic therapy to a mammal comprising administering an effective amount of a hpG-CSF polypeptide having an amino acid sequence selected from the group consisting of:

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+1                                  +10                                 +20
Thr Pro Leu Gly Pro Ala Ser Ser  Leu  Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
                                +30                                 +40
Val Arg Lys Ile  Gln  Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys
                           +50                                 +60
Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly  His Ser Leu Gly  Ile Pro  Trp Ala  Pro
                      +70                                 +80
Leu  Ser Ser Cys Pro Ser Gln  Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln  Leu His Ser
                 +90                                 +100
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala  Leu Glu Gly Ile  Ser  Pro Glu Leu Gly
                           +110                                +120
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala  Asp Phe Ala Thr Thr  Ile  Trp Gln Gln
                      +130                                +140
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro  Thr Gln Gly Ala Met Pro Ala Phe
                 +150                                +160
Ala Ser Ala  Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser  His Leu Gln  Ser Phe
                      +170                 +174
Leu Glu Val Ser Tyr Arg Val Leu  Arg His Leu Ala Gln Pro;
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and

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-1   +1                             +10                                 +20
Met  Thr Pro Leu Gly Pro Ala Ser Ser  Leu  Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
                                +30                                 +40
Val Arg Lys Ile  Gln  Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys
                           +50                                 +60
Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly  His Ser Leu Gly  Ile Pro  Trp Ala  Pro
                      +70                                 +80
Leu  Ser Ser Cys Pro Ser Gln  Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln  Leu His Ser
                 +90                                 +100
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala  Leu Glu Gly Ile  Ser  Pro Glu Leu Gly
                           +110                                +120
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala  Asp Phe Ala Thr Thr  Ile  Trp Gln Gln
                      +130                                +140
Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro  Thr Gln Gly Ala Met Pro Ala Phe
                 +150                                +160
Ala Ser Ala  Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser  His Leu Gln  Ser Phe
                      +170                 +174
Leu Glu Val Ser Tyr Arg Val Leu  Arg His Leu Ala Gln Pro;
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> and analogs thereof wherein one or more cysteine residues located at positions 17, 36, 42, 64, and 74 are replaced by serine.

Dependent claim 3 relates to the use of that claimed therapy in conjunction with chemotherapy:

> Claim 3 of the '823 patent: A method of claim 2 wherein said therapy is in conjunction with chemotherapy.

III. OVERVIEW OF THE INTRINSIC RECORD

A. Summary of the '755 and '823 Patents' Disclosure

Dr. Souza's '755 and '823 patents share the same patent specification, which differs only with respect to the claims of each patent. The Background Section of the common patent specification describes the prior art efforts of others to obtain protein preparations they alternately called "pluripoietin," "pluripotent CSF," or "CSF-ß."[18] While these prior art preparations exhibited activity in *in vitro* assays, none of them enabled the identification of the chemical structure of any active substance they contained, or the treatment of patients suffering from neutropenia. As Dr. Souza's patent specification aptly states, the cancer cell cultures used to obtain the prior art preparations did not provide an adequate or suitable source for a therapeutic product:

> To the extent that hpG-CSF may prove to be therapeutically significant and hence need to be available in commercial scale quantities, isolation from cell cultures is unlikely to provide an adequate source of material. It is noteworthy, for example, that restrictions appear to exist against commercial use of Human Tumor Bank cells such as the human bladder carcinoma cell line 5637 (A.T.C.C. HTB9) which have been reported as sources of natural hpCSF isolates in Welte, et al. (1985, supra).[19]

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[18] Ex. 1 ('755 patent, col. 2:4-60).

[19] Ex. 1 ('755 patent, col. 3:7-15).

The limitations of G-CSF from human cancer cells heightened the need for a new and different approach to produce the sought after therapeutic product, such as the recombinant DNA methods described in Dr. Souza's patent specification. This method also provided a new human G-CSF product that was separated from contaminants associated with the G-CSF produced by human cancer cells grown in culture.

The patents-in-suit describe how Dr. Souza was able to: (1) clone and determine the nucleotide sequence of a DNA encoding the particular 174 amino acid species of human G-CSF; (2) create genetically engineered cells to produce recombinant G-CSF in abundance; (3) produce an isolated 174 amino acid species of human G-CSF; and (4) disclose that this recombinant G-CSF was capable of increasing the production and/or release of granulocytes. The disclosure of each of these inventive steps resulted in a series of patents issued in Dr. Souza's name, including the '755 and '823 patents-in-suit.

As described in the patents-in-suit, Dr. Souza overcame many hurdles in successfully obtaining human G-CSF in a quantity and quality for therapeutic use. In order to clone a DNA encoding human G-CSF, Dr. Souza needed to first obtain a partial amino acid sequence of the human G-CSF polypeptide. Example 1(A) of the patents-in-suit describes three attempts to obtain a suitable amino acid sequence from a prior art preparation provided by the Welte research group at Sloan Kettering Institute in New York, but each attempt failed to provide useful sequence information.[20] Example 1(B) describes how Dr. Souza produced a new cell line and his own culture method and how he improved upon known methods of purifying human G-CSF to obtain a more substantially pure human G-CSF preparation.[21] The human G-CSF produced by Dr. Souza was of sufficient quantity and quality to enable him to obtain a sequence

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[20] Ex. 1 ('755 patent, col. 6:1-54).

[21] Ex. 1 ('755 patent, col. 6:55 – col. 8:1).

of 44 amino acid residues from the N-terminal of the protein as listed in Table IV of the patents.[22] This sequence provided a starting point for Dr. Souza's attempts to clone a DNA encoding human G-CSF.[23] Dr. Souza's cloning work is reported in Examples 2-4 and includes the preparation of a cDNA library,[24] a novel design for a probe set to account for the degeneracy of the sequence,[25] and the successful isolation of both cDNA and genomic clones encoding human G-CSF.[26] Once Dr. Souza had obtained and confirmed the correct nucleotide sequence of the DNA encoding human G-CSF, he used a DNA sequence to identify the 174 amino acid species of human G-CSF.[27]

As described in Examples 6, 7 and 9 of the patents-in-suit, the next important step was to prepare recombinant, genetically engineered cells that would produce biologically active human

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[22] *See* Ex. 1 ('755 patent, col. 8:32-47).

[23] DNA cloning refers to a process of isolating a targeted DNA sequence from a cell and then producing multiple copies of it. DNA is a nucleic acid comprised of four different bases or "nucleotides" (designated A, T, G and C. As shown in Figure 2 of the patents, these DNA nucleotides can be grouped in sets of three (or codons) to designate the coding of the DNA sequence for a corresponding sequence of amino acids. Each triplet of nucleotides codes for a single amino acid, but the "degeneracy" of the genetic code refers to the fact that most amino acids are coded for by multiple codons or triplets of DNA – some amino acids are encoded by as many as six different codons. Thus, by knowing the coding sequence of a DNA, one can determine the sequence of amino acids coded for by that DNA, but the reverse is not true. Because of the degeneracy of the genetic code, knowing the amino acid sequence does not reveal the particular DNA sequence that may be present in a cell and producing that protein.

[24] Ex. 1 ('755 patent, col. 8:51 – col. 9:32). A cDNA library contains DNA sequences that are complementary to the mRNAs produced in the cell. When proteins are made by cells, the protein coding regions of the cell's DNA are copied by a process called transcription into messenger RNA or "mRNA" (also a nucleic acid and similar to DNA) which the cell then uses as a template for protein production through a process called translation in which the polypeptide chain of amino acids is assembled according to the sequence coded in the mRNA.

[25] Ex. 1 ('755 patent, col. 9:35 – col. 10:62) (several inosines were introduced in the probe design in the third or wobble position of the codon to account for the degeneracy of the coding sequence).

[26] Ex. 1 ('755 patent, col. 10:63 – col. 12:34) (genomic DNA is that DNA taken from the cell's genome and is more complex than cDNA because of the interspersing of protein coding regions with non-coding regions).

[27] Ex. 1 ('755 patent, col. 11:66 – col. 12:3).

G-CSF in quantities sufficient for therapeutic use. To accomplish this result, appropriate DNA sequences were prepared and cells selected and manipulated to produce the 174 amino acid species of human G-CSF in a form and at a level of production that would prove to be therapeutically effective when administered to humans. Dr. Souza's application disclosed how to manipulate mammalian and bacterial cells to exclusively produce the particular 174 amino acid species of human G-CSF claimed in his '755 patent.[28]

As disclosed in the patent, when human proteins are produced recombinantly in bacteria, typically, the protein is produced with an additional amino acid, methionine ("Met") at the beginning (or N-terminal) of the polypeptide.[29] So, Dr. Souza's patent claims also include this "Met-174" form of the human G-CSF polypeptide. In Example 8 of the patents, Dr. Souza also disclosed the creation of analogs of the 174 amino acid sequence where cysteines (one of the 22 standard amino acids) were replaced by serines (another of the 22 standard amino acids),[30] and certain of these analogs are recited in the claims.

The patent disclosure continues to describe the characterization of the physical and biological properties of Dr. Souza's recombinant human G-CSF products. Example 10 reports on the molecular weight of the recombinant human G-CSF products and the results of various *in vitro* and *in vivo* assays. In particular, Dr. Souza showed that his human G-CSF induced the differentiation of a leukemia cell line,[31] and the proliferation and differentiation of human bone

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[28] Ex. 1 ('755 patent, col. 13:23 – col.19:33).

[29] Ex. 1 ('755 patent, col. 14:65 – col. 15:2). This addition of Met occurs because of the need to have an ATG codon (which codes for Met) as the translation initiation sequence.

[30] Ex. 1 ('755 patent, col. 16:66 – col. 17:63).

[31] Ex. 1 ('755 patent, col. 20:37-50) (WEHI-3B D^{+}).

marrow cells.[32] The patent also discloses that when Dr. Souza's human G-CSF was injected into hamsters, it caused a significant increase in the production and/or release of granulocytes.[33]

Dr. Souza also disclosed novel therapeutic treatments using the claimed human G-CSF polypeptide products:

> Polypeptide products of the present invention may be useful, alone or in combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders, such as aplastic anemia. They may also be useful in the treatment of hematopoietic deficits arising from chemotherapy or from radiation therapy. The success of bone marrow transplantation, for example, may be enhanced by the application of hpG-CSF. Wound healing burn treatment and the treatment of bacterial inflammation may also benefit from the application of hpG-CSF. In addition, hpG-CSF may also be useful in the treatment of leukemia based upon a reported ability to differentiate leukemic cells.[34]

As a result of all of Dr. Souza's inventions, the medical community today possesses therapeutically effective pharmaceutical compositions for treatment of neutropenia.

B. Prosecution of the Asserted Patents

Dr. Souza filed his priority patent application ("the '959 Application") on August 23, 1985 — disclosing and claiming, *inter alia*, an "hpG-CSF" polypeptide having the specific 1-174 amino acid sequence and methods of treatment utilizing that polypeptide.[35] What followed was a

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[32] Ex. 1 ('755 patent, col. 20:52 – col. 21:48).

[33] Ex. 1 ('755 patent, col. 24:12-29).

[34] Ex. 1 ('755 patent, col. 4:41-53).

[35] *See, e.g.*, Ex. 11 (8/23/85 '959 Application) at AMT_00000006-055 pending claim 7 ("A polypeptide according to claim 1 possessing part or all of the primary structural conformation of human pluripotent granulocyte colony-stimulating factor as set forth in Table VII [setting forth the 1-174 sequence] or any naturally occurring allelic variant thereof."); pending claim 31 ("A synthetic polypeptide having part or all of the amino acid sequence as set forth in Table VII and having one or more of the in vitro biological activities of naturally-occurring pluripotent granulocyte colony-stimulating factor."); pending claim 36 ("A method for providing hematopoietic therapy to a mammal comprising administering an effective amount of a polypeptide according to claims 1 or 34.").

lengthy and complex patent prosecution that included an interference proceeding with two other groups of researchers that had filed patent applications on G-CSF preparations isolated from human cancer cells. Because Dr. Souza's patent application described and claimed multiple, patentably distinct inventions, the Patent Office required Amgen to prosecute these separate inventions in separate patents .[36] After years of careful scrutiny, the Patent Office recognized the many inventions disclosed in Dr. Souza's patent applications by issuing multiple separate patents, each assigned to Amgen, including the '755 and '823 patents at issue here.

Throughout the prosecution that resulted in the issuance of the '755 and '823 patents, Dr. Souza highlighted the distinguishing characteristics of his invention over the prior art preparations:

> [N]aturally occurring human G-CSF is not a viable human therapeutic product (only trace amounts have been obtained); the product of the invention on the other hand, has been proven to be clinically effective, and is the first therapeutic product which can be used to effectively treat the hundreds of thousands of chemotherapy patients who suffer from a dangerous drop in white blood cell count, and to treat other disorders involving low white blood cell counts.[37]

Initially, the Examiner rejected Dr. Souza's claims as being directed to the same protein contained in prior art preparations obtained from human cancer cells grown in culture, as described in *Welte et al.*, Pro. Natl. Acad. Sci. (U.S.A.) 82:1526-1530 (1985) and *Nicola et al.*, Nature 314:625-628 (1985).[38] In response to the Examiner's rejections, Dr. Souza explained that

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[36] See Ex. 12 ('548 Application Prosecution History, 3/15/88 Examiner's Action, Paper No. 9) at AMT_00000917-920.

[37] Ex. 13 ('755 Prosecution History, 5/29/90 Amendment D, Paper No. 9) AMT_00002355-369 at p. 9.

[38] Ex. 14 ('755 Prosecution History, 12/29/89 Examiner's Action, Paper No. 7) AMT_00002325-351 at p. 12; *see also* Ex. 15 ('823 Prosecution History, 11/13/95 Examiner's, Action Paper No. 4) AMT_00001249-255 at p. 6.

his invention was to the particular 1-174 human G-CSF species, whereas Nicola and Welte's preparations also contained the less active 177 amino acid species of human G-CSF.

Following the filing of Dr. Souza's '959 Application, other researchers cloned the DNA encoding another species of human G-CSF having 177 amino acids.[39] These researchers also reported that the prior human G-CSF preparations derived from cancer cells grown in culture contained a mixture of both 174 and 177 species of human G-CSF.[40]

Distinguishing the prior cancer cell preparations, Dr. Souza explained that the polypeptide disclosed and claimed in his patent application "is a homogenous composition ***containing only 174 amino acid residues and is entirely free of the less active G-CSF 177 amino acid species***."[41] Dr. Souza further informed the Examiner that the pending claims were "conspicuously different from any of the natural products isolated from the 5637 cell line of Welte et al. and Nicola et al. in that they are a ***single species of human G-CSF polypeptide having 174 amino acid residues***, optionally having an N-terminal methionyl residue."[42]

The Examiner initially rejected Souza's claims as unpatentable over *Ono et al.*, U.S. Patent No. 4,833,127 ("the '127 patent"). Dr. Souza again distinguished the cell line recited in

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[39] Ex. 10 (Nagata et al., "Molecular cloning and expression of cDNA for human granulocyte colony-stiumulating factor," *Nature* 319:415-417 (1986)) AMT_00011216-218. The 177 amino acid sequence differed from the sequence earlier disclosed by Dr. Souza by the addition of three amino acids inserted after position 35 of the sequence identified by Dr. Souza.

[40] Ex. 16 (Nagata et al., "The chromosomal gene structure and two mRNAs for human granulocyte colony-stimulating factor," *EMBO Journal* 5(3):575-581 (1986)) AMT_00010929-935.

[41] Ex. 17 ('755 Prosecution History, 6/2/95 Preliminary Amendment F, Paper No. 27) AMT_00002426-432 at p. 5 (emphasis added).

[42] *Id*. AMT_00002426-432 at p. 4.

the '127 patent because it "produce[d] two G-CSF polypeptide species; one having 174 amino acid residues and the other having 177 amino acid residues."[43]

As a result, the Examiner understood the claims to be directed to a particular species of human polypeptide, separated from the 177 G-CSF species:

> The following is an Examiner's Statement of Reasons for Allowance: . . . Claims 55 and 57 (renumbered as 1 and 2) are deemed free of the prior art, since the prior art always disclosed mixtures of two forms of hpG-CSF (174 and 177 amino acids in length, respectively), whereas Applicant has accomplished separation of the two forms via recombinant expression, and the claims are directed to as such.[44]

The Examiner issued the '755 patent on December 3, 1996, and shortly afterwards, the same Examiner issued the '823 patent on December 10, 1996.

During the course of prosecution, the Patent Office declared a three-way interference involving claims by Welte, Ono, and Dr. Souza to human G-CSF products. Dr. Souza moved for judgment of no interference-in-fact on the ground that Souza's human G-CSF product was patentably distinct from Welte's and Ono's human G-CSF products produced by cancer cells grown in culture. Dr. Souza demonstrated that his human G-CSF product contained only the 174 amino acid G-CSF species, whereas Welte's and Ono's human G-CSF products were mixtures of the 174 and 177 amino acid human G-CSF species.[45] After initially opposing Souza's motion, Ono later withdrew his opposition and filed a statutory disclaimer of the Ono '127 patent.[46] The

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[43] Ex. 17 ('755 Prosecution History, 6/2/95 Preliminary Amendment F, Paper No. 27) AMT_00002426-432 at p. 6.

[44] Ex. 18 ('755 Prosecution History, 12/4/95 Notice of Allowability, Paper No. 31) AMT_00002462-465 at p. 4.

[45] Ex. 19 ('396 Interference, 5/20/91 Motion of Souza for Judgment on the Grounds that there is no Interference in Fact, Paper No. 19) at AMT_00008276-309.

[46] Ex. 20 ('396 Interference, 6/1/92 Abandonment of Contest, Paper No. 204) at AMT_00014553-557.

Patent Office's Board of Patent Appeals and Interferences subsequently granted Dr. Souza's motion for judgment of no interference-in-fact, "for the reasons stated therein."[47] Because Dr. Souza's human G-CSF product was determined to be patentably distinct from Welte's human G-CSF product, both Dr. Souza and Welte were permitted to continue prosecution of their respective patent applications.[48]

Thus, the prior art preparations were disclosed to the Patent Office and expressly distinguished during interference and prosecution proceedings. The Patent Office granted the asserted claims after years of careful scrutiny because Dr. Souza directed his claims to a particular species of human polypeptide that differed from and did not encompass the prior art preparations.

IV. LEGAL PRINCIPLES OF CLAIM CONSTRUCTION

The scope and meaning of patent claims is a question of law "exclusively within the province of the Court" to determine.[49] "The words of a 'claim are generally given their ordinary and customary meaning'" which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention."[50] Importantly, that person of ordinary skill in the art is deemed to have read the claim term in context of the entire intrinsic record, including the specification and prosecution history.[51] Thus, where the intrinsic record unequivocally shows that the patentee imparted special meaning to a term or relinquished claim

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[47] Ex. 21 ('396 Interference, 7/8/92 PTO Communication re Judgment now appropriate, Paper No. 205) at AMT_00014560.

[48] Ex. 22 ('396 Interference, 7/8/92 Judgment, Paper No. 206) at AMT_00014561-562.

[49] *Markman v. Westview Instruments*, 517 U.S. 370, 372 (1996).

[50] *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (citations omitted).

[51] *Id.* at 1313.

scope, the patentee's express representations will control.[52] For example, "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs."[53]

The Federal Circuit has adopted a claim construction framework that favors intrinsic evidence, "*i.e.*, the patent itself, including the claims, the specification and, if in evidence, the prosecution history."[54] First and foremost, the claim construction analysis begins with the claims themselves,[55] as the claims define that which "the patentee is entitled the right to exclude."[56] However, the "claims 'must be read in view of the specification, of which they are a part.'"[57] The Federal Circuit in *Phillips* highlighted the primacy of the specification in the claims construction analysis, noting that "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'"[58]

A review of the prosecution history is also of "primary significance,"[59] as it "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the

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[52] *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003).

[53] *Phillips*, 415 F.3d at 1316.

[54] *Vitronics Corp.*, 90 F.3d at 1582 ("Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language."); *Phillips*, 415 F.3d at 1318.

[55] *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998) ("There is a hierarchy of analytical tools. The actual words of the claim are the controlling focus.").

[56] *Innova/Pure Water, Inc. v. Safari Water Filtration Sys.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004); *Phillips*, 415 F.3d at 1312 ("It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'").

[57] *Phillips*, 415 F.3d at 1315 (quoting *Markman*, 52 F.3d at 978).

[58] *Id.* (quoting *Vitronics Corp.*, 90 F.3d at 1582).

[59] *Markman*, 52 F.3d at 980 ("This 'undisputed public record' of proceedings in the Patent and Trademark Office is of primary significance in understanding the claims.").

claim scope narrower than it would otherwise be."[60] The role of the prosecution history in claim construction is well established in Supreme Court and Federal Circuit precedent.[61]

V. AMGEN'S PROPOSED CONSTRUCTIONS[62]

Amgen's proposed constructions for '755 claim 1 and '823 claim 2 are shown in the tables below:

`755 Patent Claims 1 and 2	
Claim Limitation	Amgen's Proposed Construction
"An isolated human pluripotent granulocyte colony stimulating factor (hpG-CSF) polypeptide having an amino acid sequence selected from the group consisting of: +1 +10 Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro +20 Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln +30 Val Arg Lys Ile Gln Gly Asp Gly Ala Ala +40 Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys +50 Leu Cys His Pro Glu Glu Leu Val Leu Leu +60	An isolated species of human polypeptide, designated hpG-CSF, having an amino acid sequence selected from A. the 1-174 amino acid sequence: +1 +10 Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro +20 Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln +30 Val Arg Lys Ile Gln Gly Asp Gly Ala Ala +40 Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys +50 Leu Cys His Pro Glu Glu Leu Val Leu Leu +60 Gly His Ser Leu Gly Ile Pro Trp Ala Pro

[60] *Phillips*, 415 F.3d at 1317 (citing *Vitronics Corp.*, 90 F.3d at 1582-83).

[61] *Goodyear Dental v. Davis*, 102 U.S. 222, 227 (1880) (holding that a claim construction can be "confirmed by the avowed understanding of the patentee, expressed by him, or on his half, when his application for the original patent was pending."); *Graham v. John Deere Co.*, 383 U.S. 1, 33 (1966) ("[C]laims that have been narrowed in order to obtain the issuance of a patent by distinguishing the prior art cannot be sustained to cover that which was previously by limitation eliminated from the patent."); *Omega Eng'g, Inc.*, 334 F.3d at 1324.

[62] Amgen's proposed claim constructions are attached hereto in chart form as Appendix A.

Gly His Ser Leu Gly Ile Pro Trp Ala Pro
+70
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
+80
Leu Ala Gly Cys Leu Ser Gln Leu His Ser
+90
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
+100
Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly
+110
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
+120
Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
+130
Met Glu Glu Leu Gly Met Ala Pro Ala Leu
+140
Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
+150
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
+160
Val Leu Val Ala Ser His Leu Gln Ser Phe
+170
Leu Glu Val Ser Tyr Arg Val Leu Arg His
+174
Leu Ala Gln Pro;

and

-1 +1

+10
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro
+20
Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
+30
Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
+40
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys
+50
Leu Cys His Pro Glu Glu Leu Val Leu Leu
+60
Gly His Ser Leu Gly Ile Pro Trp Ala Pro
+70
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
+80
Leu Ala Gly Cys Leu Ser Gln Leu His Ser
+90
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
+100
Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly
+110
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
+120
Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
+130
Met Glu Glu Leu Gly Met Ala Pro Ala Leu
+70
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
+80
Leu Ala Gly Cys Leu Ser Gln Leu His Ser
+90
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
+100
Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly
+110
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
+120
Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
+130
Met Glu Glu Leu Gly Met Ala Pro Ala Leu
+140
Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
+150
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
+160
Val Leu Val Ala Ser His Leu Gln Ser Phe
+170
Leu Glu Val Ser Tyr Arg Val Leu Arg His
+174
Leu Ala Gln Pro;

B. the above 1-174 amino acid sequence with an additional Met at position -1; and

C. analogs of the above sequences wherein one or more cysteine residues located at positions 17, 36, 42, 64, and/or 74 are replaced by serine.

Gln Pro Thr Gln Gly Ala Met Pro Ala Phe +140 Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly +150 Val Leu Val Ala Ser His Leu Gln Ser Phe +160 Leu Glu Val Ser Tyr Arg Val Leu Arg His +170 Leu Ala Gln Pro; +174 and analogs thereof wherein one or more cysteines residues located at positions 17, 36, 42, 64, and 74 are replaced by serine."	

`823 Patent Claims 2, 3 and 4	
Claim Limitation	Amgen's Proposed Construction
"a hpG-CSF polypeptide having an amino acid sequence selected from the group consisting of: +1 +10 Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro +20 Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln +30 Val Arg Lys Ile Gln Gly Asp Gly Ala Ala +40 Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys +50 Leu Cys His Pro Glu Glu Leu Val Leu Leu +60 Gly His Ser Leu Gly Ile Pro Trp Ala Pro +70 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln +80 Leu Ala Gly Cys Leu Ser Gln Leu His Ser +90 Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln +100 Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly +110 Pro Thr Leu Asp Thr Leu Gln Leu Asp Val +120	a species of human polypeptide, designated hpG-CSF, having an amino acid sequence selected from A. the 1-174 amino acid sequence: +1 +10 Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro +20 Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln +30 Val Arg Lys Ile Gln Gly Asp Gly Ala Ala +40 Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys +50 Leu Cys His Pro Glu Glu Leu Val Leu Leu +60 Gly His Ser Leu Gly Ile Pro Trp Ala Pro +70 Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln +80 Leu Ala Gly Cys Leu Ser Gln Leu His Ser +90 Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln +100 Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly +110 Pro Thr Leu Asp Thr Leu Gln Leu Asp Val

Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
+130
Met Glu Glu Leu Gly Met Ala Pro Ala Leu
+140
Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
+150
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
+160
Val Leu Val Ala Ser His Leu Gln Ser Phe
+170
Leu Glu Val Ser Tyr Arg Val Leu Arg His
+174
Leu Ala Gln Pro;

and

-1 +1

+10
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro
+20
Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
+30
Val Arg Lys Ile Gln Gly Asp Gly Ala Ala
+40
Leu Gln Glu Lys Leu Cys Ala Thr Tyr Lys
+50
Leu Cys His Pro Glu Glu Leu Val Leu Leu
+60
Gly His Ser Leu Gly Ile Pro Trp Ala Pro
+70
Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
+80
Leu Ala Gly Cys Leu Ser Gln Leu His Ser
+90
Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln
+100
Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly
+110
Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
+120
Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
+130
Met Glu Glu Leu Gly Met Ala Pro Ala Leu
+140
Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
+150
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
+160
Val Leu Val Ala Ser His Leu Gln Ser Phe
+170
Leu Glu Val Ser Tyr Arg Val Leu Arg His
+174
Leu Ala Gln Pro;

+120
Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln
+130
Met Glu Glu Leu Gly Met Ala Pro Ala Leu
+140
Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
+150
Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
+160
Val Leu Val Ala Ser His Leu Gln Ser Phe
+170
Leu Glu Val Ser Tyr Arg Val Leu Arg His
+174
Leu Ala Gln Pro;

B. the above 1-174 amino acid sequence with an additional Met at position -1; and

C. analogs of the above sequences wherein one or more cysteine residues located at positions 17, 36, 42, 64, and/or 74 are replaced by serine.

and analogs thereof wherein one or more cysteines residues located at positions 17, 36, 42, 64, and 74 are replaced by serine."	

A. "A[] . . . human pluripotent granulocyte colony stimulating factor (hpG-CSF) polypeptide" ('755 claims 1 and 2, '823 claims 2 and 3)

The asserted claims of the '755 and '823 patents recite the term "a[] . . . human pluripotent granulocyte colony stimulating factor (hpG-CSF) polypeptide." The '755 patent claims further recites that the polypeptides of the claim are "isolated." The term "a[] . . . human pluripotent granulocyte colony stimulating factor (hpG-CSF) is a designation or name coined by Dr. Souza to refer to the newly identified polypeptides encoded by DNA sequences that he first cloned and characterized from human cells — the 174 amino acid sequence polypeptide recited the claims.[63] Dr. Souza also ascribed this name to the factor present in the prior art preparations obtained from human cancer cells because "[b]ased upon their common properties" he believed his 174 amino acid polypeptide was present in those preparations.[64] The specification confirms that "an hpG-CSF," as used in and further defined in the asserted claims, is merely a name for a sequence-defined polypeptide. Figure 2 shows a recombinant cDNA sequence cloned by Dr. Souza and the encoded human polypeptide having the defining 1-174 sequence of amino acids.[65] The specification refers to this clone and encoded amino acid sequence as "hpG-CSF."[66]

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[63] Ex. 1 ('755 patent, col. 3:18-20). Assigning a polypeptide name to an amino acid sequence was and is a common practice in the art and provides a convenient and practical means to refer to a polypeptide, and even DNA encoding it, without having to repeat cumbersome sequence information each time.

[64] Ex. 1 ('755 patent, col. 2:61-65).

[65] Ex. 1 ('755 patent, col. 4:66-67 ("FIG 2. shows the sequence of recombinant hpG-CSF cDNA clone Ppo2.") and Ex. 1 ('755 col. 11:48 – col. 12:3).

[66] Ex. 1 ('755 patent, col. 3:19-22 ("According to the present invention, DNA sequences coding for all or part of hpG-CSF are provided."); '755 patent, col. 11:48 – col. 12:3; col. 25:6-8) ("[T]he DNA sequence described herein . . . encodes hpG-CSF polypeptides")).

Further, the term "hpG-CSF" is used to refer to polypeptides having the 174 amino acid core sequence with an alanine instead of a threonine at the first position: "Yields of [Ala^{1}]hpG-CSF from the culture supernatant were on the order of 1 to 2.5 µg/ml."[67] It is also used to refer to polypeptides having the common 174 amino acid core with one cysteine residue replaced by a serine residue:

> [Ser^{17}]hpG-CSF, [Ser^{36}]hpG-CSF, [Ser^{42}]hpG-CSF, [Ser^{64}]hpG-CSF, and [Ser^{74}]hpG-CSF products prepared according to Example 9 were assay[ed] for hpG-CSF activity in the 3H-thymidine uptake, CFU-GM, and WEHI-3B D+ assays.[68]

Lastly, the term "hpG-CSF" is used in the specification to refer to polypeptide analogs that arise from or are variations of the common 174 amino acid core sequence:

> In addition to naturally-occurring allelic forms of hpG-CSF, the present invention also embraces other hpG-CSF products such as polypeptide analogs of hpG-CSF and fragments of hpG-CSF.[69]

As noted above, Dr. Souza's patent specification discloses a breadth of potential activities and uses for the polypeptides of his invention. The patent specification recites that Dr. Souza's polypeptide inventions could have "one or more of the biological properties (e.g., immunological properties and in vitro biological activity" of naturally occurring hpG-CSF.[70] But since Dr. Souza's polypeptides are defined by their sequences, the specification emphasizes that there is no standard set of biological properties required for any of the claimed polypeptides:

> It is noteworthy that *activity is not necessary* for any one or more of the products of the invention to have therapeutic utility . . . or utility in other contexts, such as in assays of hpG-CSF antagonism.

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[67] Ex. 1 ('755 patent, col. 19:1-3).

[68] Ex. 1 ('755 patent, col. 23:66 – col. 24:3).

[69] Ex. 1 ('755 patent, col. 24:31-34).

[70] Ex. 1 ('755 patent, col. 4:1-8).

> Competitive antagonists may be quite useful in, for example, cases of overproduction of hpG-CSF.[71]

During prosecution, Dr. Souza made clear that his claimed hpG-CSF polypepetide was distinguished by its amino acid sequence:

> The present invention relates to applicant's discovery of the biochemical identity of the hematopoietic protein, pluripotent granulocyte colony-stimulating factor and *its characterization by means of its amino acid sequence*.[72]

B. "having an amino acid selected from the group consisting of . . . ." ('755 claims 1 and 2, '823 claims 2 and 3)

Claim 1 of the '755 patent and claim 2 of the '823 patent expressly define the claimed "hpG-CSF" as a polypeptide being limited by the specified amino acid sequences: "hpG-CSF polypeptide having an *amino acid sequence selected from the group consisting of*." The claims go on to recite the specific amino acid sequences that fall within the claimed species of human polypeptide, which all have or arise from the common 174 amino acid core sequence. The claimed amino acid sequences all relate to the core 1-174 amino acid sequence set forth in Figure 2 of the specification. Together, these recited sequences define a singular species of human polypeptide, designated "hpG-CSF."[73]

The claims of the '755 and '823 patents recite particular sequences. Each of the recited amino acid sequences bears the requisite relation to the 1-174 core amino acid sequence. The first amino acid sequence (listed as "A" in the chart) represents the 1-174 amino acid core sequence depicted in Figure 2. The second amino acid sequence (listed as "B" in the chart) —

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[71] Ex. 1 ('755 patent, col. 24:66 – 25:5) (emphasis added).

[72] Ex. 23 ('643 Prosecution History, 6/8/87 Amendment A and Reply, Paper No. 8) AMT_00000901-916 at p. 5 (emphasis added).

[73] These polypeptides are considered "human" in that the 174 amino acid core sequence on which they are based was first cloned from human cells. As the specification demonstrates, these "human" polypeptides can nonetheless be generated outside of human cells (e.g., in bacterial cells). *See* Ex. 1 ('755 patent, col. 4:8-23).

which the specification describes as being a product of recombinant expression in bacteria[74] — is a variation that includes a methionine residue added to the front end of the 1-174 human amino acid core sequence. The third amino acid sequence (listed as "C" in the chart) — which are also described as being made and expressed through recombinant DNA technology — are specific substitution analogs of the human 1-174 amino acid core sequence where a serine residue is substituted for a cysteine residue at specific positions in the core sequence.

The prosecution history highlights that the human 174 amino acid core sequence and specific recited variations thereof make up a single species of human polypeptides. During prosecution, Dr. Souza characterized his claimed invention as: "[t]he polypeptides of Applicant's new claims 55-56 [issued as claims 1 and 2] . . . are a single species of human G-CSF polypeptide having 174 amino acid residues, optionally having an N-terminal methionyl residue"[75] and that "new claims 55-56 are directed to isolated 174 amino acid species of G-CSF and specific analogs thereof."[76] Thus, the claim language, the specification and the prosecution history establish that this single species of human polypeptide encompasses a defined group of sequences based on a common human 174 amino acid sequence.

As mentioned above, it was discovered after the filing of Dr. Souza's original patent application that the human G-CSF gene can generate two species of human G-CSF polypeptides.[77] One human G-CSF polypeptide species has the 174 amino acid core sequence that Dr. Souza identified. The other human G-CSF polypeptide species, which was not identified

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[74] *E.g.*, Ex. 1 ('755 patent, Fig. 7; col. 5:10-12; col. 15:17-21; col. 15:52-59; Table X).

[75] Ex. 17 ('755 Prosecution History, 6/2/95 Preliminary Amendment F, Paper No. 27) AMT_00002426-432 at p. 4.

[76] Id.

[77] Ex. 10 (Nagata et al., "Molecular cloning and expression of cDNA for human granulocyte colony-stimulating factor," *Nature* 319:415-417 (1986)) AMT_00011216-218.

by Dr. Souza, has a 177 amino acid sequence.[78] The 174 amino acid species is distinguishable from the 177 amino acid species by the internal absence of three contiguous amino acids — an absence that shifts the sequential positioning of the nearly 140 amino acids that follow it.[79] Based on this discovery and confirmation that prior art cell lines contained mRNA encoding both the 174 and 177 species, it was understood that the alleged prior art preparations of human G-CSF contained a mixture of Dr. Souza's 174 amino acid "hpG-CSF polypeptide," as further defined by the recited amino acid sequences in the claim, and the other naturally-occurring 177 amino acid species of human G-CSF polypeptide.

That Dr. Souza's invention is directed to just his single species of "hpG-CSF polypeptide" was first brought to the fore during a three-way interference proceeding between Dr. Souza, Dr. Welte and Mr. Ono before the Patent Office. There it was established that Dr. Souza should not be a party to the interference proceeding because his inventions were patentably distinct from those of the other patent applicants. Specifically, it was argued that Dr. Souza's inventions were directed to a single species of human polypeptide, whereas the inventions of the other applicants were directed to preparations that contained, at least, a mixture of Dr. Souza's claimed "hpG-CSF polypeptide" and the less active 177 amino acid G-CSF species. In a motion distinguishing his inventions, Dr. Souza defined his invention as being only the 174 species of human G-CSF:

> The human G-CSF product of Souza's claims 51 and 52 is a ***homogeneous composition containing only the 174 amino acid human G-CSF species polypeptide***, and is entirely free of the less active human G-CSF polypeptide species.[80]

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[78] Id.

[79] Ex. 16 (Nagata et al., "The chromosomal gene structure and two mRNAs for human granulocyte colony-stimulating factor," *EMBO Journal* 5(3):575-581 (1986)) AMT_00010929-935.

[80] Ex. 19 ('396 Interference, 5/20/91 Motion of Souza under 37 C.F.R. §1.633(b) for Judgment on the Ground that there is no Interference in Fact) AMT_00008276-309 at ¶ 15.

> The DNA sequence disclosed in Figure 2 and employed according to the disclosures of Souza's application ***encodes only the 174 amino acid human G-CSF polypeptide species*** and cannot be used to prepare a human G-CSF polypeptide species having 177 amino acid residues.[81]

The PTO granted Dr. Souza's motion "for the reasons stated therein."[82]

This issue arose again during prosecution of the '755 patent claims. The Examiner did not initially appreciate that Dr. Souza's "hpG-CSF polypeptide" species was defined exclusively in terms of its amino acid sequence. Looking to such other properties as approximate molecular weight and biological activity, the Examiner rejected the pending claims to "a[n] isolated . . . hpG-CSF polypeptide" as covering prior art preparations that the Examiner suggested "appear[] to be the same."[83] Dr. Souza's pending claims, however, were successfully distinguished from the prior art based on the nature of his claimed "hpG-CSF polypeptide."

First, Dr. Souza reemphasized the very point he had made to end his involvement in the interference — that "naturally occurring G-CSF products" are "mixtures of two species of polypeptide having, respectively, 174 or 177 amino acids."[84] Next, Dr. Souza explained that his claimed hpG-CSF polypeptide covered only one single species of human polypeptides:

The polypeptides of Applicant's new claims 55-56 are conspicuously different from any of the natural products isolated from the 5637 cell line of Welte et al. and Nicola et al. in that

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[81] *Id.* ¶ 13 (emphasis added).

[82] Ex. 21 ('396 Interference, PTO Communication re Judgment now appropriate, Paper No. 205) at AMT_00014560. Ono originally opposed the motion, but later withdrew his opposition.

[83] Ex. 14 ('755 Prosecution History, 12/29/89 Office Action) AMT_00002325-351; *see also* Ex. 15 ('823 Prosecution History, 11/13/95 Office Action) AMT_00001249-255.

[84] Ex. 17 ('755 Prosecution History, 6/2/95 '298 Continuation Application and Preliminary Amendment) AMT_00002426-432. Souza then drew the distinction between the two forms of G-CSF, explaining that "the natural G-CSF product comprises a mixture of about 80% of the 174 amino acid species and 20% of the 177 amino acid species, with the latter having only about 5% of the biological activity of the former." *Id.*

they are a *single species* of human G-CSF polypeptide having 174 amino acid residues, optionally having an N-terminal methionyl residue.[85]

It was emphasized that Dr. Souza's "isolated" species is not only homogenous with respect to his specifically recited polypeptide variants, but precludes mixtures having the 177 G-CSF species:

Applicant's G-CSF polypeptide as disclosed in Figure 2 is a homogenous composition containing only 174 amino acid residues and is entirely free of the less active G-CSF 177 amino acid species.[86]

The Examiner then understood that Dr. Souza's innovative use of recombinant methods had allowed him to not simply separate a 174/177 *mixture* of human G-CSF from other non-G-CSF human proteins, but to separate the claimed 174 amino acid human G-CSF species from the unclaimed 177 amino acid human G-CSF species (a feat that had never been accomplished before):

Claims 55 and 57 (renumbered as 1 and 2) are deemed free of the prior art, since the prior art always disclosed mixtures of two forms of hpG-CSF (174 and 177 amino acids in length, respectively), whereas *Applicant has accomplished separation of the two forms via recombinant expression*, and the claims are directed to as such.[87]

These points were made again during prosecution of the '823 patent, this time for claims reciting methods of treatment using the same "hpG-CSF" polypeptide of the '755 patent.[88]

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[85] Ex. 17 ('755 Prosecution History, 6/2/95 '298 Continuation Application and Preliminary Amendment) AMT_00002426-432 (emphasis added).

[86] Ex. 17 ('755 Prosecution History, 6/2/95 '298 Continuation Application and Preliminary Amendment) AMT_00002426-432 (emphasis added).

[87] Ex. 18 ('755 Prosecution History, 12/4/95 Notice of Allowability, Paper No. 31) AMT_00002462-465 (emphasis added).

[88] *See* Ex. 24 ('127 Application Prosecution History, 2/13/96 Amendment C and Request for Reconsideration, Paper No. 5) AMT_00006043-050 at p. 3 ("The instant application . . . is directed to a method of providing granulocytopoietic therapy with the ***same G-CSF***

There Dr. Souza stated that "Claim 45 [issued as Claim 2], as amended, is directed to a method for providing granulocytopoietic therapy to a mammal comprising an effective amount of a ***particular*** 174 amino acid hpG-CSF polypeptide species or Met^{-1} analog thereof."[89] Dr. Souza also described the polypeptide of Claim 2 as "the 174 amino acid species," as distinct from other species of human protein in the prior art: "[T]he hpG-CSF polypeptide comprising the 174 amino acid sequence according to claim 45 [issued as Claim 2] is not the protein of the prior art."[90] He further explained that the proteins cited by the Examiner had always existed as "a mixture of distinct 174 and 177 amino acid species."[91] In contrast, Dr. Souza emphasized that the polypeptide of Claim 2 is limited to only the "174 amino acid species."[92]

C. "isolated" ('755 claims 1 and 2)

Amgen submits that the term isolated in '755 claim 1 has its plain and ordinary meaning of "set apart" or "standing alone." In the context of claim 1, "isolated" modifies "hpG-CSF polypeptide," and therefore it reinforces that the claimed polypeptides are separate from hpG-CSF polypeptides not having the amino acid sequences recited in the claim, *i.e.*, the claims do not encompass the 177 form. This meaning is consistent with the use of the term isolated in the specification and the prosecution history.

For the foregoing reasons, and in accordance with the intrinsic record, the claim limitations "an isolated human pluripotent granulocyte colony stimulating factor (hpG-CSF) polypeptide having an amino acid sequence selected from the group consisting of: [1-174]; and

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polypeptide subject matter as recited in the recently allowed claims of Serial No. 08,459,298.") (emphasis added).

[89] Ex. 24 ('127 Application Prosecution History 2/13/96 Amendment C and Request for Reconsideration, Paper No. 5) AMT_00006043-050 (emphasis added).

[90] *Id.*

[91] *Id.*

[92] *Id.*

[Met 1-174]; and serine replacement analogs" ('755 claims 1 and 2) and "a hpG-CSF polypeptide having an amino acid sequence selected from the group consisting of: [1-174]; and [Met 1-174]; and serine replacement analogs" ('823 claims 2 and 3) should be construed by this Court to mean "an isolated species of human polypeptide, designated hpG-CSF" and "a species of hpG-CSF polypeptide, designated hpG-CSF," respectively, as further defined by the specific amino acid sequences, and as recited in the claim, based on the core 1-174 amino acid sequence disclosed in Figure 2 of the specification.

D. "A method for providing granulocytopoietic therapy to a mammal" ('823 claims 2 and 3)

The asserted '823 claims are directed to "a method for providing granulocytopoietic therapy to a mammal."

'823 Claim 2	
Claim Limitation	Amgen's Proposed Construction
A method for providing granulocytopoietic therapy to a mammal comprising	A method for therapeutically treating a mammal by stimulating the production of granulocytes comprising

The preamble of '823 Claim 2 embodies an essential characteristic of Dr. Souza's invention claimed in the '823 patent — the ability to provide therapy. The method claim is more than just administering a polypeptide. Rather, the preamble states that the method must provide therapy to a mammal by stimulating the production of granulocytes. As such, the preamble is "necessary to give life, meaning, and vitality" to the claim and it must be construed as a claim limitation.[93] Indeed, the Federal Circuit instructs that a preamble is a limitation where it

[93] *Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002).

provides an antecedent basis or gives meaning and purpose to subsequent steps recited in the body of the claim.[94] Here, in the absence of the preamble's stated objective to provide granulocytopoietic therapy to a mammal, the term "effective amount" in the body of Claim 2 is empty language.[95]

In construing the preamble, the focus is on the phrase "granulocytopoietic therapy to a mammal." The first word of the claim phrase, "granulocytopoietic," was expressly defined in the prosecution history to mean the development of granulocytes. Dr. Souza told the Patent Office:

Although the term 'granulocytopoietic' does not appear *in ipsis verbis* in the specification, the term is clearly understood to mean the development of granulocytes and the specification discloses that G-CSF has predominantly granulocyte colony-stimulating activity.[96]

Consistent with this prosecution statement, the specification discloses that Dr. Souza's "hpG-CSF" polypeptide "produces a specific enhancement of production and/or release of granulocytes in a mammal."[97] The intrinsic record thus demonstrates that the term "granulocytopoietic" means stimulating the production of granulocytes.[98]

The second part of the claim phrase, "therapy to a mammal," requires that the claimed method be used to therapeutically treat a mammal. The specification discloses that "hpG-CSF"

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[94] *See Vizio, Inc. v. Int'l Trade Comm.*, 605 F.3d 1330, 1340-41 (Fed. Cir. 2010).

[95] *See Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002) ("In the absence of the preamble's stated objective to diagnose thrombosis, the term 'test subject' is empty language. What is one testing for, and who is a suitable subject?").

[96] Ex. 24 ('127 Application Prosecution History, 2/13/96 Amendment C and Request for Reconsideration, Paper No. 5) AMT_00006043-050 at p. 4.

[97] Ex. 1 ('755 patent, col. 24:28-29).

[98] The intrinsic definition of "granulocytopoietic" is also consistent with the plain meaning at time of the invention. Ex. 25 (Dorland's Illustrated Medical Dictionary (1981)) defines "granulocytopoietic" as "pertaining to, characterized by, or stimulating granulocytopoiesis." "Granulocytopoiesis" in turn means "the production of granulocytes." Ex. 25 (Dorland's Illustrated Medical Dictionary (1981)).

can be used in many therapeutic treatments to prevent, cure, or alleviate life-threatening conditions, such as hematopoietic disorders and hematopoietic deficits arising from chemotherapy or from radiation therapy.[99] Other disclosed therapeutic uses of "hpG-CSF" include its use to enhance success of bone marrow transplantation, provide wound healing burn treatment to treat bacterial inflammation, and to treat leukemia.[100]

Indeed, the ability of the recited "hpG-CSF" polypeptides to provide therapeutic treatment was a point of distinction over the prior art materials. During prosecution of the related '755 product claims, Dr. Souza explained that while "naturally occurring human G-CSF is not a viable therapeutic product," the product of the present invention "has been proven to be clinically effective, and is the first therapeutic product which can be used to effectively treat the hundreds of thousands of chemotherapy patients who suffer from a dangerous drop in white blood cell counts, and to treat other disorders involving low white blood cell counts."[101]

Based on the intrinsic record, the claim phrase "[a] method for providing granulocytopoietic therapy to a mammal" means "[a] method for therapeutically treating a mammal by stimulating the production of granulocytes."

E. "administering an effective amount of" ('823 claims 2 and 3)

The method of '823 Claim 2 requires the administration of "hpG-CSF" in an amount that is both adequate and suitable for therapeutic use.

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[99] Ex. 1 ('755 patent, col. 4:41-47).

[100] Ex. 1 ('755 patent, col. 4:48-53).

[101] Ex. 13 ('755 Prosecution History, 5/29/90 Amendment D, Paper No. 10) AMT_00002355-369 at p. 9 (emphasis added).

'823 Claim 2	
Claim Limitation	Amgen's Proposed Construction
administering an effective amount of	administering an amount adequate and suitable for therapeutic use of

Dr. Souza was the first to invent, disclose, and make available a human G-CSF product in an amount and quality that was suitable for therapeutic use:

> Prior to the invention, G-CSF was only available in minute quantities (principally by means of isolation from extremely low concentration natural sources). . . . Recombinant methods were carried out by the inventor which allowed for large scale production of pure G-CSF by cells in culture which assured that enough G-CSF could be made available for human clinical trial now in progress, in the treatment of patients undergoing chemotherapy.[102]

Reading the "effective amount" limitation in conjunction with the preamble, the meaning of the claim term plainly refers to the amount effective to therapeutically treat a mammal by stimulating the production of granulocytes.[103] That is, '823 claim 2 requires that "hpG-CSF" be present in a sufficient quantity *and* quality to prevent, cure, or alleviate life-threatening, and debilitating conditions in a mammal by stimulating the production of granulocytes. The

[102] Ex. 26 ('755 Prosecution History, 3/31/89 Byrne Declaration Accompanying Petition to Make Special); Ex. 13 ('755 Prosecution History, 5/29/90 Amendment D, Paper No. 10) AMT_00002355-369 at p. 9 ("[N]aturally occurring human G-CSF is not a viable human therapeutic product (only trace amounts have been obtained); the product of the invention on the other hand, has been proven to be clinically effective, and is the first therapeutic product which can be used to effectively treat the hundreds of thousands of chemotherapy patients who suffer from a dangerous drop in white blood cell count, and to treat other disorders involving low white blood cell counts.").

[103] *See, e.g.*, *Rapoport v. Dement*, 254 F.3d 1053, 1061 (Fed. Cir. 2001) (holding that the claimed step of administering an effective amount must be analyzed in context of the preamble's stated purpose).

specification confirms this construction. In the words of the patent, pharmaceutical compositions "useful in hpG-CSF therapy" must comprise "effective amounts" of hpG-CSF.[104]

In addition, Dr. Souza's representations to the Examiner during prosecution make clear that the "effective amount" limitation requires the administration of not just any species of human G-CSF, but the "particular" 174 amino acid species of human G-CSF:

Claim 45 [issued as Claim 2], as amended, is directed to a method for providing granulocytopoietic therapy to a mammal comprising an effective amount of a *particular* 174 amino acid hpG-CSF polypeptide species or Met^{-1} analog thereof.[105]

Therefore, the plain meaning of the claim phrase "administering an effective amount," construed in the context of the entire claim, means "administering an amount adequate and suitable for therapeutic use."

VI. CONCLUSION

For the foregoing, Amgen's constructions as set forth above and in Appendix A should be adopted by the Court.

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[104] Ex. 1 ('755 patent, col. 4:24-27).

[105] Ex. 24 ('127 App. Prosecution History 2/13/96 Amendment C and Request for Reconsideration, Paper No. 5) AMT_00006043-050 (emphasis added).

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CERTIFICATE OF SERVICE

I, David J. Wolfsohn, hereby certify that on this 23rd day of July, 2010, I caused a true and correct copy of the foregoing **Amgen Inc.'s Claim Construction Brief** to be served via CM/ECF and email on the following:

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